



## Combat casualties undergoing lifesaving interventions have decreased heart rate complexity at multiple time scales<sup>☆,☆☆</sup>

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### ABSTRACT

**Purpose:** We found that heart rate (HR) complexity metrics such as sample entropy (SampEn) identified patients with trauma receiving lifesaving interventions (LSIs). We now aimed (1) to test a multiscale entropy (MSE) index, (2) to compare it to single scale measures including SampEn, and (3) to assess different parameter values for calculation of SampEn and MSE.

**Methods:** This was a study of combat casualties in an emergency department in Iraq. Electrocardiograms of 70 acutely injured adults were recorded. Twelve underwent LSIs and 58 did not. Lifesaving interventions included endotracheal intubation (9), tube thoracostomy (9), and emergency transfusion (4). From each electrocardiogram, a segment of 800 consecutive beats was selected. Offline, R waves were detected and R to R interval time series were generated. Sample entropy, MSE, and time domain measures of HR variability (mean HR, SD, the proportion of pairs of consecutive NN intervals that differ by more than 20 and 50 milliseconds, square root of the mean of the squares of differences between adjacent NN intervals) were computed.

**Results:** Differences in mean HR (LSI:  $111 \pm 33$ , non LSI:  $90 \pm 17$  beats/min) were not significant. Systolic arterial pressure was statistically but not clinically different (LSI:  $123 \pm 19$ , non LSI:  $135 \pm 19$  mm Hg). Sample entropy (LSI:  $0.90 \pm 0.42$ , non LSI:  $1.19 \pm 0.35$ ;  $P < .05$ ) and MSE index (LSI:  $2.58 \pm 2.55$ , non LSI:  $5.67 \pm 2.48$ ;  $P < .001$ ) differed significantly.

**Conclusions:** Complexity of HR dynamics over a range of time scales was lower in high risk than in low risk combat casualties and outperformed traditional vital signs.

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### 1. Introduction

This study was motivated by the need for enhanced vital sign monitoring in emergency combat casualty care. In 2009, Martin and colleagues [1] analyzed 151 deaths at a combat support hospital (CSH) in Iraq; most occurred within 1 hour of admission, either from head injury or from hemorrhage. Opportunities for improving risk assessment were noted in almost half of the cases, related to delays in hemorrhage control during transportation or in resuscitation

efforts. Earlier detection of hemorrhagic shock implies a need for improvements in the timely use and diagnostic accuracy of vital sign monitors [2]. To improve current vital sign monitors, without adding new sensors or boxes to the medic's kit, we are examining the use of computational tools that characterize and quantify the variability of beat to beat fluctuations in heart rate (HR) time series for risk stratification. Our underlying hypothesis is that information about the integrity of the body's neuroautonomic control mechanisms is encoded in the way that the HR spontaneously changes over time and that illness or injury impairs these mechanisms in ways that can be measured.

Specifically, we have applied measures of irregularity such as approximate entropy (ApEn) [3] and sample entropy (SampEn) [4], to the analysis of time series comprising between 100 and 800 heart beats [5–7]. We have referred to these as measures of HR complexity. Heart rate complexity was lower in civilian patients with trauma from the Trauma Vitals USA database who received prehospital lifesaving interventions (LSIs) than that in those who did not [8]. Heart rate complexity was also lower in patients with trauma who went on to die than that in survivors [9]. Quantification of the degree of

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complexity, using SampEn and/or ApEn, consistently outperformed traditional vital signs such as the mean HR, blood pressure (BP), or peripheral saturation of oxygen in identifying critically injured patients with trauma [8,9].

In the present study, we applied a recently described method for quantifying HR complexity, multiscale entropy (MSE). The rationale for MSE is as follows. Complex time series are typically highly irregular, but not all irregular time series are complex. For example, random signals such as those obtained by shuffling any sequence of numbers may be very variable but carry, by construction, no information. Thus, these shuffled sequences are not complex. Truly complex signals such as those produced by healthy physiologic systems, are far from random; instead, they exhibit complex patterns on multiple time scales. The information encoded on these multiple time scales is not adequately captured by ApEn or SampEn, which quantify the irregularity of a signal. To help obviate this limitation, a more generalized method called MSE was introduced [10,11]. As the name implies, MSE quantifies entropy over multiple time scales. By doing so, MSE can distinguish random signals from truly complex ones (<http://physionet.org/tutorials/cv/>). In this study, we computed both SampEn and MSE, along with traditional HR variability (HRV) metrics (described below). We also computed quadratic SampEn (QSampEn), a refinement of the original SampEn statistic, as described in the Appendix.

The goals of this study were 2 fold. First, we sought to test the hypothesis that MSE would be lower in combat casualties who undergo an LSI upon arrival to the CSH emergency department (ED) than that in those who do not. Second, we sought to elucidate the implications of selecting different parameter values for the calculation of SampEn and MSE, using very short segments of data obtained under conditions of battlefield trauma where extreme variations in HR dynamics are observed.

## 2. Materials and methods

### 2.1. Subjects

This study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board, in accordance with the approved protocol, and in compliance with the Helsinki Declaration. The study was performed under provisions of waived consent. We acquired continuous electrocardiogram (ECG) recordings from a convenience sample of combat casualties arriving at the US Army CSH located at Ibn Sina Hospital, Baghdad, Iraq, during the recent conflict. The ECGs were obtained based on the availability of a deployed research team at this hospital. Data on a total of 101 patients were collected. Of these, 31 were excluded: 20 patients had ECGs of at least 200 but less than 800 beats; 2 patients had no ECGs; 9 patients had ECGs which were very short or very noisy. These exclusions left 70 complete data sets, consisting of at least 800 beats of EKG without noise or ectopy. Of these 70 casualties, 12 patients underwent LSIs in the CSH ED (LSI group) and 58 (non LSI group) did not. Only LSIs performed in the ED were considered in this study. The list of potential LSIs included cardiopulmonary resuscitation, cricothyroidotomy, endotracheal intubation, needle decompression of pneumothorax, pericardiocentesis, emergency transfusion, tube thoracostomy, and cardioversion.

### 2.2. Data acquisition and analysis

Upon admission to the ED, casualties were placed on a PIC 50 vital signs monitor (Welch Allyn, Skaneateles Falls, NY). These monitors had an analog to digital data acquisition rate of 375 Hz. Previous work by Voss et al [12] confirmed that a sampling rate of 128 Hz or greater was sufficient for nonlinear measures of HRV. Electrocardiogram data were recorded on standard digital memory cards. Other

patient data were retrospectively recorded on paper by the deployed research team. The memory cards and the case report forms were then mailed to the US Army Institute of Surgical Research, Fort Sam Houston, Tex, for analysis. WinCPRS software (Absolute Aliens OY, Turku, Finland) was used to process the ECGs and to identify the R waves. A trained analyst then reviewed every R wave detected and made corrections as needed, selecting 800 beats of clean ECG from each data set. WinCPRS software then outputted the R to R (RR) interval time series. In these 800 beat data sets, each R wave represented a normal sinus (N) rhythm beat. (Therefore, the RR interval time series are identical to the NN interval series.) We wrote custom software in Java and C++ to perform all subsequent HR dynamics calculations.

### 2.3. Measures

We calculated standard time domain metrics of HRV: mean HR, SD of the normal to normal beats, the square root of the mean squared differences of consecutive NN intervals, and the proportion of pairs of consecutive NN intervals that differ by more than 20 and 50 milliseconds [13–15]. We calculated single scale (SampEn, QSampEn) and multiscale (MSE) entropies as detailed in the Appendix.

### 2.4. Statistical analysis

Statistical analysis was done using SAS v. 9.1 (SAS Institute, Cary, NC). *t* or Wilcoxon tests were performed to analyze continuous variables, and  $\chi^2$  tests were used to analyze categorical variables, as appropriate. Significance was accepted at  $P < .05$ .

## 3. Results

Lifesaving interventions performed included endotracheal intubation (9), tube thoracostomy (9), and emergency transfusion (“Code Red”) (4). There was 1 death in the LSI group and none in the non LSI group. Basic clinical information for the LSI and non LSI patients are presented in Table 1.

Heart rate variability time domain measures are presented in Table 2. The average time between consecutive NN intervals trended lower for the LSI group, that is, the HR was faster, compared with the non LSI group. However, this difference was not statistically significant ( $P = .07$ ). All standard time domain measures of HRV were significantly lower for the LSI than for the non LSI group.

SampEn, QSampEn, and MSE index values are presented in Table 3.

Sample entropy, calculated using the most widely used parameter values ( $m = 2$  and  $r = 20\%$  of the SD of the time series), showed reduced RR interval irregularity for the LSI group compared with the non LSI group. Statistically, even more robust separation between the 2 groups was seen when SampEn was computed for a fixed  $r$  value of 6 milliseconds and  $m = 2$ . The MSE index, which

**Table 1**  
Basic patient data

Variable	LSI (n = 12)	Non-LSI (n = 58)
Age (y)	23 ± 15	27 ± 10
Sex (male)	12 (100%)	52 (89%)
Blunt or explosive mechanism	1 (8.3%)	19 (32%)
HR (beats/min)	111 ± 33	90 ± 17
SAP (mm Hg)	123 ± 19*	135 ± 19
GCS <sub>total</sub>	12 ± 5**	15 ± 0
GCS <sub>motor</sub>	5 ± 2**	6 ± 0

Data are means ± SD. LSI indicates patients who did receive LSIs; non-LSI, patients who did not receive LSIs; blunt/explosive mechanism, number of patients in each group injured by a blunt or explosive mechanism; SAP, systolic arterial pressure.

\*  $P < .05$ .

\*\*  $P < .001$ .

**Table 2**  
HRV time-domain measures

Variables	LSI	Non-LSI	P
AVNN	0.589 ± 0.185	0.694 ± 0.135	.067
SDNN	0.023 ± 0.013	0.038 ± 0.020	.022
rMSSD	0.009 ± 0.008	0.019 ± 0.014	.005
pNN20	7.13 ± 13.71	22.20 ± 22.77	.006
pNN50	0.91 ± 2.84	5.42 ± 10.83	.018

Values of HRV time-domain measures for the LSI and non-LSI groups. AVNN indicates average of all normal-to-normal (NN) intervals, in seconds; SDNN, SD of all NN intervals, in seconds; rMSSD, square root of the mean of the squares of differences between adjacent NN intervals, in seconds; pNN20 and pNN50, percentage of differences between adjacent NN intervals that are greater than 20 and 50 seconds, respectively.

incorporates the SampEn values for scales 1 to 4, was significantly lower for the LSI than for the non LSI group. The MSE index also provided more robust separation between groups than SampEn used as a single scale measure.

Of note, comparable results were obtained for SampEn calculated with fixed  $r$  values ranging from 3 to 10 milliseconds, for  $m = 1$ , and for  $m = 3$ . In addition, comparable results were obtained with the QSampEn measurement.

#### 4. Discussion

The principal finding in this study was that combat casualties who underwent LSIs in the ED of a CSH in Iraq had lower HR complexity than those who did not. This difference held across multiple time scales, as quantified by the MSE method. We have previously reported lower HR complexity in seriously injured patients and animals by use of 2 closely related, single scale measures: SampEn and ApEn. To our knowledge, this study is the first in which MSE has been applied to acutely injured patients and the first specific application of these techniques to combat casualties in a theater of operations.

The rationale for using MSE is as follows. The entropy of a time series is a measure of its degree of randomness or unpredictability. Sample entropy is an algorithm designed for quantifying the entropy of relatively short and noisy signals. Multiscale entropy generalizes SampEn to multiple time scales. One major advantage of using MSE over SampEn, especially for the study of physiology, is that SampEn only quantifies how random a signal is. It may fail to distinguish between complex and random signals. Multiscale entropy probes a signal on multiple time scales, that is, at various levels of resolution (<http://www.physionet.org/physiotools/mse/tutorial/>). By doing so, MSE can discriminate between truly complex signals, that is, those containing information on multiple scales, from those that are just variable. Multiscale entropy has been applied to a wide class of physiologic and biologic signals, including HR time series, intracranial pressure signals, magnetoencephalographic recordings, red blood cell flickering motions, and others, to help quantify the output

**Table 3**  
Single and MSE measures

Measures	LSI	Non-LSI	P
Single scale			
SampEn ( $r = 20\%$ )	0.90 ± 0.42	1.19 ± 0.35	.035
SampEn ( $r = 6$ ms)	0.58 ± 0.56	1.17 ± 0.59	.003
QSampEn	8.73 ± 3.40	12.58 ± 2.78	.002
Multiscale			
MSE index (scales 1–4)	2.80 ± 2.60	5.78 ± 2.45	.001

Results for entropy-based measures. Values of SampEn are presented for  $r = 20\%$  of the time series' SD and for  $r = 6$  milliseconds. Values of QSampEn (see Appendix) are presented for a minimum number of matches ( $M$ ) of 30. The MSE index, defined as the summation of SampEn values for scales 1 to 4, is presented. In all cases, the parameter  $m$  was set to 2. See text for details.

of systems controlled by regulatory mechanisms operating on multiple time scales [16–19].

When applied to the cardiovascular system, MSE integrates information about the processes underlying the control of the HR. High MSE values are consistent with the notion that the processes controlling the HR in healthy subjects operate over multiple time scales. For example, loss of HR complexity has been reported in a number of settings with altered (dysregulated) neuroautonomic control, including chronic heart failure, aging, and acute major depressive disorder [11,20].

What is the rationale for developing complexity based vital signs for injured patients? Vital sign measurement is a core practice in prehospital, emergency, and critical care. The Centers for Disease Control and Prevention's 2011 *Guidelines for Field Triage of Injured Patients* is a revision of the American College of Surgeons Committee on Trauma's Decision Scheme. It states that the first step in triage is to measure vital signs and level of consciousness. Injured patients with a Glasgow Coma Scale (GCS) score of 13 or lower, a systolic BP less than 90 mm Hg, or a respiratory rate less than 10/min or greater than 29/min (or a requirement for ventilator support) are triaged to a trauma center, irrespective of anatomic findings or mechanism of injury [21].

Several large studies, however, have led to a reappraisal of these standard vital sign based triage criteria [22–27]. These studies have found that (i) vital sign based trauma triage, alone, is associated with a significant undertriage rate; (ii) undertriage is associated with increased mortality; (iii) vital sign ranges previously considered "normal" may actually be associated with increased mortality; (iv) predictive equations based on multiple variables outperform single vital signs in the prediction of mortality; and (v) continuous vital sign data outperform single vital signs.

Given these findings, some authors have introduced new devices into emergency care, for example, to measure lactate levels [28–30]. In the present study, we took a different approach to the diagnostic problem in trauma. We applied new mathematical methods of analysis to the beat to beat variability inherent in the HR. This approach takes advantage of the fact that the ECG is already acquired (but underused) in severely injured patients. Therefore, we sought to obtain more information from an existing sensor, rather than to add new sensors to our patients.

Our previous work included studies in animal models and in prehospital and intensive care unit (ICU) patients. In anesthetized sheep, severe hemorrhagic shock caused a decrease in the high frequency power of HRV, as well as a decrease in the ApEn and the fractal dimension of the HR [6]. We saw similar changes in anesthetized swine with hemorrhage [5], and with chest trauma followed by hemorrhage [7]. In prehospital patients with trauma, ApEn was an independent predictor of mortality, even when GCS and injury severity score were taken into account [9]. In the same database, there was no difference in HR or BP between patients undergoing an LSI and those not, but patients differed on SampEn and GCS (motor component) [8]. Low SampEn and ApEn were features of patients on admission to the burn ICU and were restored to normal values with fluid resuscitation [31]. On further analysis, we found that SampEn retained its ability to discriminate survivors from nonsurvivors in patients with prehospital trauma, even as we moved from large data sets (800 heart beats) down to much smaller data sets (100 heart beats) [32].

In the present study, we again note lower SampEn in patients undergoing LSIs. In addition, we extend these findings by detecting lower HR complexity at multiple time scales as documented by MSE. In patients with trauma, there are at least 2 physiologically based explanations for this finding. One is that hypovolemia causes a loss of HR complexity through a vagally mediated process, related to compensatory withdrawal of parasympathetic tone to the heart. This mechanism would explain, for example, the decrease in high frequency and short term time domain HRV measures, which often

accompany the decrease in HR complexity. The other explanation is that brain injury or ischemia may cause a loss of HR complexity through central nervous system mediated processes. The latter mechanism would explain the lower mean GCS score observed in the LSI vs non LSI patients in this study. Of note, HR complexity has been proposed as an indicator of the overall adaptiveness and plasticity of the HR control system, rather than as a diagnostic test for any specific type of injury.

In this study, we also extended previous analyses by exploring different methodological approaches for choosing the parameter  $r$  for calculation of SampEn and the MSE index. Specifically, we compared the results using a fixed  $r$  value (based on the sampling frequency of the original ECG data) with those obtained using the “standard” implementation (based on an arbitrary percent [eg, 15% 20%] of each time series’ SD). We found that for HR analysis, the use of the fixed  $r$  value provided better discrimination for group comparisons using either single or multiscale measures. Furthermore, we found that in cases of very low time series variance, sole reliance on the SD based method could lead to spuriously high values of SampEn or MSE because of “pseudo fluctuations” generated by discretization errors. This problem is particularly relevant in trauma conditions, in which low HR variance is most prevalent. Finally, we note that the computation of MSE, not just traditional SampEn (equivalent to scale 1 of MSE), provides a more general assessment of HR complexity and allows discrimination of irregularity caused by random variations with low information content (eg, R R fluctuations with atrial fibrillation) vs R R fluctuations with intrinsically higher information content (eg, sinus rhythm dynamics in healthy subjects with intact neuroautonomic control) [10,11,20].

Several other groups have contributed to the study of complex HRV in critical illness. Norris et al [33] reported an increase “cardiac uncoupling” (defined by a higher percentage of 5 minute intervals within 24 hours for which the HR SD fell within the range 0.3 to 0.6 beats/min) in patients with trauma who died in the ICU, regardless of etiology of death. Ahmad and colleagues [34] at the University of Ottawa have developed a multiparameter HRV system. In a pilot study in patients with bone marrow transplant, both SampEn and MSE (as well as other HRV metrics) decreased before the clinical diagnosis of sepsis.

Finally, Moorman and colleagues [35] studied the impact of information about HR dynamics in the neonatal ICU setting. They have developed a real time index, termed *HR characteristics*, which takes into consideration multiple features of the neonatal RR interval time series [36,37]. Their randomized controlled clinical trial included 3003 very low birth weight infants, a group at increased risk for sepsis [35]. It showed that physician access to the real time HR characteristics index was associated with a significant reduction in infant mortality, from 10.2% to 8.1%. Their finding that measures of HR

dynamics in a newborn ICU setting can lead to decreased mortality presumably by increasing clinicians’ situational awareness is an important contribution to the emerging field of anticipatory medicine.

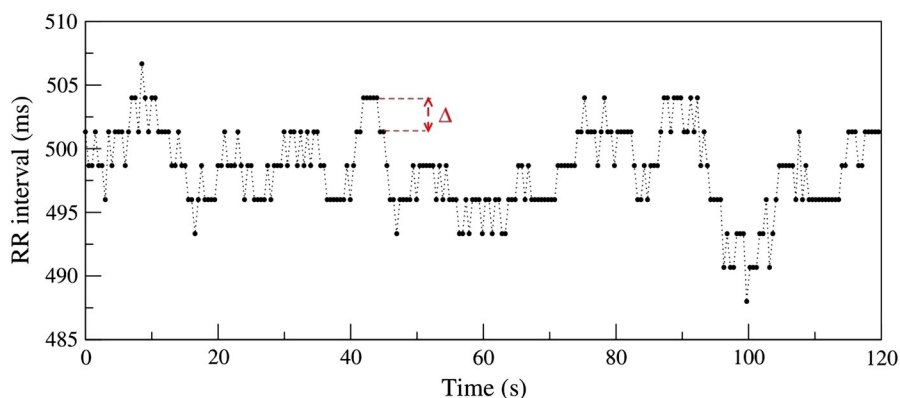
## 5. Limitations

Our study’s limitations include the relatively small sample size and the potential inaccuracies inherent in collecting data in a busy ED in a war zone. Of the 325 patients on whom some effort was made to collect ECGs under this protocol, only 70 patients had ECG of sufficient length and quality, as well as accompanying demographic data. Also, the imbalance in the number of patients in the 2 groups (12 LSI vs 58 non LSI) may introduce selection bias. We were unable to determine the relationship between the timing of LSIs and the timing of ECG collection. We also did not record whether patients received sedative medications during their ED care, which could influence HR complexity. The problem of the timing of interventions is a recurring theme in this type of research, which must be addressed in future prospective study designs. Decreased mental status is associated with the performance of LSIs in this study, manifested by differences between LSI and non LSI patients on both total GCS score ( $GCS_{total}$ ) and motor component of the GCS score ( $GCS_{motor}$ ). In the present study, the non LSI group is essentially a group with normal  $GCS_{total}$  and  $GCS_{motor}$  scores of  $15 \pm 0$  and  $6 \pm 0$ , respectively. This observation is consistent with our previous findings in patients with prehospital trauma [9]. Prehospital and post ED data were also lacking. Unfortunately, prehospital data from the battlefield have been notoriously difficult to obtain. It will be of great interest to study changes in MSE and other HRV measures over time, in response to therapy.

Finally, future studies should also use real time (as opposed to offline, post hoc) calculation of HR complexity. Once a sufficient number of heart beats have been recorded, the entropy algorithms take only about 1 second to run. Sample entropy computation can be performed as soon as the first 100 beats have been collected. Multiscale entropy computation can then be added as soon as the first 800 beats have been collected, serially updating the estimates as more data become available. Based on work by Moorman et al [35] and Ahmad et al [34], we are confident that such real time computation is technologically quite feasible.

## 6. Conclusions

The amount of complex irregularity in beat to beat fluctuations in the HR can be quantified by SampEn. Multiscale entropy extends this measure to progressively longer time scales. In this study, we found that lower SampEn and MSE index were associated with the



**Fig. 1.** Time series of the RR intervals for a patient who underwent a lifesaving intervention. The discretization interval  $\Delta = 1/375 = 2.7$  milliseconds is the inverse of the sampling frequency of 375 Hz. Note that the RR intervals are multiples of  $\Delta$ : 488, 490.7, 493.3, 496, 498.7, 501.3, 504, and 506.7 milliseconds. The time series’ SD is 3.6 milliseconds. Note that in this case, 20% of the SD is 0.72 milliseconds  $< \Delta$ . Therefore, the number of matches obtained with  $r = 20\%$  of the SD is the same as with  $r = 0$  milliseconds.

performance of LSIs in combat casualties arriving at an ED in a combat zone. We also found that careful selection of the  $r$  parameter based on the ECG sampling rate significantly improves the ability of both SampEn and MSE index to discriminate such patients. Prospective studies of these “new vital signs” are needed to establish their potential role in clinical assessment and management of critically injured patients.

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## Appendix

### Single scale entropy measurement

We implemented a previously published algorithm for SampEn [4]. Briefly, SampEn is a conditional probability measure; it quantifies the likelihood that if a sequence of  $m$  consecutive data points matches (within a tolerance  $r$ ) a template sequence of the same length, then the 2 will still match when their length increases from  $m$  to  $m + 1$  data points.

Selection of the  $r$  parameter is important for determining the entropy of a signal, for the following reasons. SampEn quantifies the degree of signal irregularity. Both the correlation properties and the variance (energy) of the signal contribute to its entropy. Among signals of equal variance, those generated by uncorrelated random processes are the most entropic. In addition, among signals with the same correlation properties, those with higher amplitude (ie, larger SD) are the most entropic. As explained below, different ways of selecting the  $r$  value for the calculation of SampEn may weight one property more than the other.

For the calculation of SampEn, 2 data points,  $NN_i$  and  $NN_j$ , with different numerical values, for example, 800 and 802 milliseconds, may be considered indistinguishable if the level of accepted noise is below their absolute difference – in this case, 2 milliseconds. The value of the parameter  $r$  sets this “tolerance” level. If  $|NN_i - NN_j| > r$ , then  $NN_i \neq NN_j$ ; otherwise,  $NN_i = NN_j$ .

For physiologic signal analysis,  $r$  is commonly chosen as a percentage (15%–20%) of the time series' SD, a procedure equivalent to normalizing the time series to unit variance before calculating SampEn. This implementation assures that the value of SampEn is the same for all time series generated by the same dynamical process despite possible differences in the amplitude of their fluctuations. This approach is necessary for comparing the entropy of the fluctuations generated by 2 different regulatory systems, for example, HR and body temperature. Because the amplitude range and units of these fluctuations are *not* comparable, prior normalization of the time series is required. However, the choice of  $r$  as a percentage of SD is problematic when some of the time series' SDs are very low. In such cases, the 15%–20% “rule” may yield values that are below the resolution (quantization level,  $\Delta$ ) of the time series (Fig. 1).

In this study, the ECG recordings were acquired at a sampling frequency of 375 Hz. Thus, the time ( $\Delta$ ) between 2 consecutive ECG voltage values is  $\Delta = 1/375 \sim 2.7$  milliseconds. Furthermore, each RR

interval, as well as the difference between any 2 RR intervals, is a multiple of  $\Delta$  (see Fig. 1).

The SDs of the time series analyzed here varied between 5 and 63 milliseconds. When  $r$  is set to 20% SD, for some time series, SampEn will be calculated with  $r = 1$  millisecond and for others with  $r = 12.6$  milliseconds. When  $r = 1$  millisecond, 2 RR intervals, for example, 800 and 802, will be “seen” as different from each other. However, when  $r = 12.6$  milliseconds, 2 other intervals, for example, 800 and 812, will be “seen” as equal. Choosing  $r$  as a percentage of the SD effectively implies accepting different levels of noise for the analysis of different subjects. Furthermore, in this study, the “20% rule” yielded  $r$  values below the discretization level  $\Delta$  for 7 of the 70 time series analyzed. In these cases, using  $r = 20\%$  SD yielded the same results as  $r = 0$ . Generally stated, the values of SampEn obtained for  $r$  in the interval  $n\Delta \leq r < (n + 1)\Delta$  are the same as for  $r = n\Delta$ .

An alternative solution to the problem of selecting an appropriate  $r$  value is to choose a single fixed value for all the time series that is greater than the discretization level [20]. In this study, we chose  $r = 6$  milliseconds. This implementation does not “discount” the contributions to the entropy values that arise from differences in the time series' variances, but importantly does insure that the level of noise accepted is the same for all data sets.

Lake and Moorman [38] sought to solve the problem of selecting the  $r$  value by converting the calculation of the conditional probability that goes into the definition of SampEn to that of a density. They introduced the *QSampEn*, which they defined as  $QSampEn = SampEn + \ln(2r)$ . Quadratic SampEn does not depend on the value of  $r$  but on the minimum number of required matches ( $M$ ). In this study, we also calculated *QSampEn* values for  $M = 30$ .

The  $m$  value reflects the extension of local correlations in the data. The  $m$  value is often chosen as the first zero of the autocorrelation function. For the analysis of RR intervals time series,  $m = 2$  is the most common choice and the one adopted here.

### Multiple scale entropy measurement

Multiscale entropy quantifies the degree of irregularity (measured using SampEn) of a time series over multiple time scales. Time series that are highly irregular – thus, more entropic over a broad range of scales – are considered more complex than those that show irregular behavior at only a single time scale.

The MSE algorithm consists of 3 steps: (i) coarse graining the original time series to derive multiple signals, each of which captures the system dynamics on a different scale; (ii) calculating a measure of entropy suitable for finite time series (SampEn in this case) for each coarse grained time series; and (iii) integrating the entropy values over a predefined range of scales to obtain an index of complexity (MSE index).

The element  $j$  of the coarse grained time series  $y$  for scale  $n$  is calculated according to the equation:  $y_j^{(n)} = 1/n \sum_{i=1}^n (j - i + 1)x_i$ , where  $x_i$ , with  $1 \leq i \leq N$ , are the data points of the original time series. The MSE curve is obtained by plotting SampEn for each coarse grained time series (ordinate) as a function of scale (abscissa). The length of the original time series,  $N$ , determines the largest scale,  $n$ , analyzed [10,11]. In this study, we used  $n = 4$ .

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